Alice E. Till, Ph.D.
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

August 8, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Draft Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products [Docket No. 02D-0258, 67 *Federal Register*, 45983, July 11, 2002]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing more than $30 billion in 2001 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

We welcome the opportunity to comment on the draft, revised guidance on bioavailability and bioequivalence studies for orally administered drug products and would appreciate your careful consideration of these comments (attached) as you finalize the revised guidance.

Please feel free to contact me if you have any questions.

Sincerely,

Alice E. Till

Alice E. Till, Ph.D.

CC A. L. Sanchez

Att.

02D-0258 C 8

Final Comments on FDA Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations

General Remarks

This revision to the BA/BE guidance reflects two major points: 1) removal of the replicate design recommendation for extended release products and 2) removal of the IBE and PBE criteria as a method for market access. Overall, we welcome these changes and find this version of the guidance to be a significant improvement over the October 2000 version.

The changes concerning the use of ABE for market access are welcomed. This is in line with the findings of previous research on the topic (Journal of Clinical Pharmacology, 40:561-572; 41:811-822) and we compliment the FDA on its movement to address the situation following the PharmSci Adcom in late 2001. We have no objection from a scientific perspective on changes concerning the replicate design recommendation for extended release products following the discussion at the AdCom.

Changes have also been made to clarify the FDA's recommended approaches to design, analysis, and decision-making. The guidance clarifies the FDA's definition of "proportionality" (important when seeking BE based on in vitro dissolution) and makes some changes to the FDA's thinking on the granting of biowaivers based on in vitro testing.

Specific Comments - Major

1. Page 9- III. A.8.c. and Page 23- Appendix A.
Since both AUC0-t and AUC0-inf have been requested, do both have to meet 90% CI limits 80 to 125%? It seems more appropriate for the sponsor to decide up front which AUC will be subjected to these limits when designing the protocol.

2. Pages 11 and 12, Section IV.
It may not be appropriate to use the BE limits (80-125%) for Cmax (or partial AUC for early exposure) when we compare an immediate release solid dosage to some formulations (e.g., solutions/capsules/suspensions/controlled release etc.)

3. Page 18, VI Special Topics.
The guidance should also provide specific suggestions for BA/BE study designs for highly variable drugs (either high inter- or high intra-subject variability)

Specific Comments - Minor

1. Page 4- II.C. First paragraph- "same molar dose".
It should be clarified whether potency adjustment for small variations in the assay of drug content between formulation batches is to be carried out, or whether nominal dose potency is to be used.

2. Page 7, Section III.A.1, Line 7
Please consider adding the following text:

"*Since the intra-subject variability is generally less than the inter-subject variability and a potential carry over effect is generally negligible, a crossover design is typically used for BA/BE studies.*"

3. Page 7, Section III.A.4, Line 1
Please add "crossover" to the text:

"Non replicate *crossover* study designs are recommended ....."

4. Page 8, Section 5,Line 11
Please make the following change:

"*Formal inferential* statistical analysis of subgroups is not recommended."

5. Page 10- III.A.8.c.
For computers without WordPerfect symbol fonts installed, the symbol tau in AUC0-tau is incorrectly displayed.

6. Page 24, Lines 1and 2

Replace "Ratio of means" with "Ratio of *least squares means*"
Replace "Confidence intervals" with "*90%* confidence intervals *for the ratio of means*"

7. Page 24- Attachment A, last sentence.
Regarding the rounding off of the confidence intervals: is it suggested that two decimal places always be used?

8. The terms "intrasubject" and "within subject" variability are interchanged throughout the document. Perhaps using just one term would be better.